Stochastic Dynamics Simulation of Alanine Dipeptide: Including Solvation Interaction Determined by Boundary Element Method

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ABSTRACT: A merger of the Poisson–Boltzmann equation and stochastic dynamics simulation is examined using illustrative calculations of alanine dipeptide. The boundary element method (BEM) is used to calculate the hydration forces acting on the solute molecule based on the surroundings. Computational efficiency is achieved by the use of a simple hydration model and a coarse boundary element. Nonetheless, the conformational distribution obtained from this new method is reasonable compared with other theoretical and computational results. Detailed analysis has been accomplished in terms of the hydration interactions and solvation energies. The results indicate that the new simulation method provides an obvious improvement over the conventional stochastic dynamics simulation technique. The further improvement of the hydration model and future application to large molecules are also discussed.
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Introduction

Molecular dynamics (MD) simulation is a powerful tool that has been applied to a variety of physics, chemistry, and biology systems.[1,2] However, there exist two limitations with this method: the approximations in the potential energy functions, and the lengths of the simulations. The first introduces systematic errors, and the second statistical errors. Much effort has been expended to improve the form of the potential functions and to prolong the time of simulations. For a protein embedded in aqueous solution, most of the computational time is used to calculate the interactions between solvent atoms and solute atoms as well as among solvent atoms. In many cases one is not interested in the details of the solvent atoms, but rather in its effect on the solute. Therefore, one can eliminate the explicit treatments of solvent molecules in the simulations to save large amounts of computational time. To do this requires an accurate description of potential function which includes the effects of solvent on the solute molecule. The conventional stochastic dynamics (SD) simulation without potential of mean force yields a good approximation for nonpolar solvents, but is not appropriate for polar solvents.[3] The presence of a solvent with a high dielectric constant modifies the interactions between charges considerably beyond the direct Coulombic term, as a result of the reaction field due to the medium. The influence of the reaction field on the solute is the major factor determining solute properties.

Recently, considerable progress has been made in the incorporation of solvent effects into MD or SD simulations using the Poisson–Boltzmann equation (PBE).[4–8] Zauhar has reported a technique for incorporating hydration forces into a molecular mechanics simulation,[4] in which the Coulombic interaction with the induced surface charge and the solvent boundary pressure are included. Sharp has combined solvation forces with a conventional molecular dynamics force field.[5] In Sharp's method, the solvation forces are calculated using the finite difference method for solving the PBE. Gilson and coworkers have described an efficient merger of the Poisson–Boltzmann and molecular dynamics approaches.[6,7] Using this method, the conformation distribution of dichloroethane and alanine dipeptide are reasonable, although the underlying PB solvation is simplified and the finite difference grids are coarse. More recently, we have combined the boundary element method (BEM)[9] with the stochastic dynamics simulation approach,[10] and the new method was called SDBEM simulation.[8] We have examined the reliability of this new method using the cyclic undecapeptide, cyclosporin A (CPA), as our study target. Compared with data obtained from MD and SD simulations, it can be seen that the SDBEM simulation has improved the SD simulation to a certain extent. However, a new method should be examined carefully before it is used in a more complex system. In addition, a small molecule that has been the subject of greater study is more favorable to test the levels of accuracy for the various methods.

In this article, we have selected alanine dipeptide (*N*-acetylalanyl-*N*-methyalamide) as our study target to examine our SDBEM algorithm. Alanine dipeptide has long served as one of the primary models for theoretical studies of backbone conformational equilibria in protein and peptides.[11–13] The chief internal degrees of freedom are the φ and ψ dihedral angles. The probability distributions of internal degrees of freedom found in SDBEM simulations are compared with that obtained from SD simulation. In addition, the total phase energies and solvation energies are presented for each minimum, and compared with data from the literature using various methods.[11–13] For this comparison, primary emphases are placed on the solvent's influence on the conformational equilibria of alanine dipeptide and the improvement of SDBEM compared with SD simulation. In SD simulation, this influence is only included to a certain extent by fitting of parameters in the molecular mechanics force fields.

The outline of this study is as follows. The general formula of the potential of mean force in SDBEM simulation and the simulation processes are described in the Methods section. Detailed analyses are presented in the Results section in terms of Ramachandran probabilities, electrostatic solvation energy, total phase energy, nonpolar interactions and effects of different numbers of triangles. Finally, some important points are summarized in the Discussion section.

Methods

GENERAL FORMULA

We consider the solvated alanine dipeptide with dielectric constants D_i and D_e in the interior and

exterior regions, respectively. The formula of SD for this system is given by the ordinary Langevin equation:

$$m_i \ddot{x}_i = F_i(\{x_i\}) - m_i \gamma_i \dot{x}_i + R_i(t) \qquad i = 1, 2, \ldots, N \quad (1)$$

where x_i is the Cartesian coordinate of atom i, γ_i is the atomic friction coefficient, and R_i denotes the random force. The system force F_i on atom i is derived from the potential of mean force $V_{mean}(\{x_i\})$ and has a form:

$$F_i(t) = -\partial V_{mean}(\{x_i\})/\partial x_i \quad (2)$$

where V_{mean} is the mean interaction between solute atoms which is affected by the presence of solvent atoms. It can be written as:

$$V_{mean}(\{x_i\}) = V_{int}(\{x_i\}) + V_{sol}(\{x_i\}) \quad (3)$$

where $V_{int}(\{x_i\})$ presents the internal potential of solute atom in the system, V_{sol} is the potential coming from the environment solvent. Obviously, eq. (2) can be rewritten as:

$$F_i = -\frac{\partial V_{int}(\{x_i\})}{\partial x_i} - \frac{\partial V_{sol}(\{x_i\})}{\partial x_i} = F_i^{int} + F_i^{sol} \quad (4)$$

where the internal force, F_i^{int}, is due to the interactions among the explicitly simulated atoms, and the external force, F_i^{sol}, is the hydration force originating from the environment. For an atom, i, with charge q_i, the external force may be written as:

$$F_i^{sol} = F_i^{rf} + F_i^{press} \quad (5)$$

where F_i^{rf} is the electrostatic force resulting from the reaction field generated by the solvent in which there may exist some mobile ions. This force can be decomposed into a sum of a series of interactions between the atom i (with charge q_i) and the induced surface charge by the boundary element method.[9] F_i^{press} arises from the purely mechanical pressure of the polarized solvent as it is pulled toward the solute.[4] Both the charged atom and the uncharged atom on the molecular surface will be exerted by a force due to the boundary pressure of the solvent.

Consider a smooth, closed two-dimensional surface Σ that contains the macromolecule and roughly follows its shape. Inside the surface there is the solute molecule with dielectric constant D_i, whereas outside the surface there is the medium with dielectric constant D_e. The interior potential ϕ^i satisfies the Poisson equation[8]:

$$\nabla^2 \phi_p^i = -\frac{1}{D_i} \sum_k q_k \delta(\mathbf{r}_p - \mathbf{r}_k) \quad (6)$$

where $\delta(\mathbf{r}_p - \mathbf{r}_k)$ is the delta distribution at $\mathbf{r}_k$ at which the kth charge q_k is placed. The exterior potential ϕ^e satisfy the linearized PBE:

$$\nabla^2 \phi_p^e = \kappa^2 \phi^e(\mathbf{r}_p) \quad (7)$$

where κ is the Dabye inverse screening length. The potential ϕ^i and ϕ^e should satisfy the following boundary conditions:

$$\phi = \phi^e \quad (8)$$

$$D_i \frac{\partial \phi^i}{\partial n} = D_e \frac{\partial \phi^e}{\partial n} \quad (9)$$

Eqs. (6) and (7) can be solved numerically by the boundary element method.[9] Afterwards, the interior and exterior field of molecule surface, $\mathbf{E}_i$ and $\mathbf{E}_e$, and the density of the induced polarization charge at an arbitrary point $\mathbf{r}$ on the molecular surface, $\sigma(\mathbf{r})$, can be calculated. With these values, the electrostatic force of reaction field acting on charge q_i can be obtained as:

$$\mathbf{F}_i^{rf}(\mathbf{R}) = \oiint_{\Sigma} \frac{q_i \sigma(\mathbf{r})(\mathbf{R} - \mathbf{r})}{|\mathbf{R} - \mathbf{r}|^3} d^2\mathbf{r} \quad (10)$$

where the integration is carried out over the entire molecular surface Σ.

The purely mechanical boundary pressure can be calculated based on the expression developed by Gilson and coworkers as[7]:

$$p(\mathbf{r}) = \frac{1}{8\pi}(D_e - D_i)\mathbf{E}_e \cdot \mathbf{E}_i \quad (11)$$

where $p(\mathbf{r})$ is a normal pressure exerted by solvent. Thus, the force of a solvent pressure on the ith atom is given by:

$$\mathbf{F}_i^{press} = \int -\mathbf{n}\, p(\mathbf{r}) d^2\mathbf{r} \quad (12)$$

where the integration is performed only over the portion of the solvent-accessible surface associated

with the ith atom. Therefore, both the charged atom and the uncharged atom will be exerted on the molecular surface by a force due to the boundary pressure of the solvent.

Note that the forces of charge–charge interaction of the solute are included in the empirical force field. They are given by the straightforward application of Coulombic law. In the present work, the BEM is used to calculate the hydration force terms. The detailed discussion of the SDBEM algorithm can be found in Ref. 8. The goal of the present work is to test the reliability of the SDBEM simulation.

SIMULATION PROCESSES

The link between BEM and SD simulation and the triangulation procedure has been described in Ref. 8. For the application of SDBEM, the molecular surface should be properly triangulated. Due to the arbitrary shape of the solute surface, finding a method to triangulate the molecular surface simply and successfully is still problematic. In the present work, we follow the triangulation method developed by Juffer and coworkers.[14] The triangulation of the solvent accessible surface of the molecule is performed every 20 time steps (0.01 ps) in the simulations.

Alanine ''dipeptide,'' shown in Figure 1, is a neutral molecule terminated by methyl groups, rather than by the carboxylic acid and amino groups of an amino acid. This is an appropriate choice to obtain a system that models an amino acid as part of a polypeptide chain. It has been a prototype model for several theoretical studies of proteins and peptides.[11] In the present work, the surface of dialanine is defined at the center of the probe rolling around the molecule. The atomic radii used in generating the dielectric boundary are set to their van der Waals radii given in the GROMOS package.[15] The probe radius is 0.14 nm, which represents the radius of a water molecule. The numbers of total triangles used in our SDBEM simulations are 60 and 112, respectively.

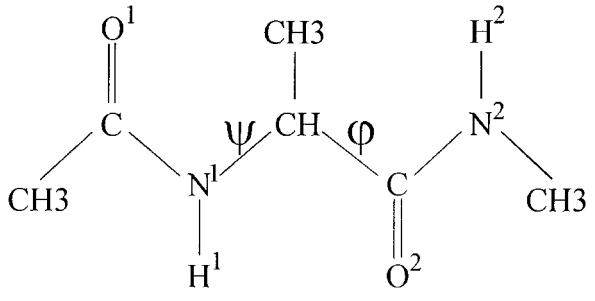

FIGURE 1. The schematic structure for alanine dipeptide, with φ and ψ torsion angles labeled.

The GROMOS force field was used for all simulations. Dielectric constants were taken as $D_i = 2$, $D_e = 80$. Nonpolar hydrogen atoms were included in the carbon atoms, whereas polar hydrogen atoms were treated explicitly. For the small molecule considered here, the internal force F_i^{int} may be evaluated rapidly. It is therefore updated with every SD dynamics time step. However, the calculation of hydration force is time consuming, and it makes sense to carry out all 20 SD dynamics time steps. After 100 steps energy minimization with steepest descents method, 100-ps SDBEM simulations were carried out for system equilibrium. Thereafter, 2-ns SDBEM simulatiaons were performed with different numbers of triangles, and the conformation trajectories were saved every 100 time steps for subsequent analysis. The time steps (0.5 fs) were taken for integrating the equation of motion. The atomic friction coefficients, $\gamma_i = \gamma_s W_i$, where γ_i is assigned 91 ps^{-1} to represent the friction coefficient of water molecule,[3] and w_i is an atomic accessible area weight factor. No cut-off radius was applied to the nonbonded interactions. The ionic strength was set to zero in all simulations. To accelerate barrier crossing, all simulations were carried out at an artificially high temperature of 1000 K. This should be borne in mind when inspecting the results of simulations. To compare these data with other work for individual conformations of the dipeptide, SDBEM simulations are also presented for cases in which the dihedral angles φ and ψ were retrained at special angles. Coupling to a pressure bath was applied to keep the system at 1 atm. The normal SD simulation was carried out under the same condition without hydration force and solvent pressure.

Results

RAMACHANDRAN PROBABILITIES

The purpose of the present work is to test the reliability of the SDBEM by comparing the results coming from SDBEM simulations and those from SD simulation. Comparisons with experimental

data, where available, are of interest but of secondary importance at the present stage of development. Once the numerical method is established, it will make sense to develop molecular parameters that optimize agreement with experimental data.

The distributions over the ϕ and ψ dihedral angles were obtained from the SD and SDBEM simulations. Results are presented in terms of normalized probability densities. The normalization requirement is:

$$W_{bin}^2 \sum_{i}^{N_{bin}} P_i = 1 \tag{13}$$

where W_{bin} is the width, in degrees of the square dihedral angle bins used in generating the two-dimensional probability distributions. N_{bin} is the number of bins and P_i is the probability density in bin i. In the present work, W_{bin} is 10° and N_{bin} is $36^2 = 1296$.

Many of quantum-mechanical calculations have provided a useful overview of the properties of the alanine dipeptide Ramachandran map in the gas phase, although the details are not expected to be fully reliable.[11] Some theoretical and calculational methods have also been used to try to estimate the solvent effects on conformational equilibria, and it is clear that the level of confidence that can be placed in these results is much lower than that in the gas phase.

Although the results calculated in the solvation show low reliability, the effects of the solvent are considered important in the influence of the equilibrium behavior of the dipeptide. When water is the solvent, two general features are almost universally observed[11]: First, the α_R region of conformation space is significantly stabilized relative to the extended forms. Second, the low-energy portions of the surface become much broader, so that the C_7^{eq} and C_5 minima found in the gas phase merge into a single broad well in the β region of the Ramachandran map.

In the SD simulation, the solvent effects are included to some extent by empirical fitting of parameters in the molecular mechanics force fields. The result of SD simulation (Fig. 2a) shows the second feature of water: a broad distribution peak at about (−95°, 105°) appears over the C_7^{eq} and C_5 conformations. However, in the α_R region, there does not exist an obvious peak in the distribution density, which demonstrates that the SD simulation cannot estimate the solvent's effect of stabilizing the α_R conformation. Figure 2b and c are the distribution densities of the SDBEM simulations using 60 and 112 triangles, respectively. Despite the different number of triangles, the agreement of two simulations is good. Besides the broad peak at (−95°, 105°) over the C_7^{eq} and C_5 conformations, the SDBEM simulation also reflects the first feature of water correctly. The key change in conformational preference in going from vacuum to water —increased population of the α_R conformation (−75°, −40°)—is well reproduced. This feature can be explained qualitatively in terms of peptide group dipole moments. α_R conformation has a large net dipole moment because the peptide dipoles are roughly parallel in this region. Therefore, this conformation can be more strongly solvated than those with smaller dipole moments. From the Ramachandran maps we can see there still exist other peaks, such as $C_7^{\alpha x}$ at about (65°, −65°). Compared with the Ramachandran probability from finite difference calculations,[6] it can be seen that the positions of distribution peaks are agreement in quality. However, the altitude and width of peaks are obviously different. This may be because we incorporate the electrostatic interaction into the GROMOS force field directly. To combine this interaction with an intrasolute force field requires a process refinement to balance the additional electrostatic term with the other terms of the force field. Although the force field of the SDBEM method should be reparameterized, its improvement is obvious compared with SD simulation. Hence, the SDBEM simulation may be more suitable to study the properties of proteins and peptides in solution than SD simulation.

ELECTROSTATIC SOLVATION ENERGY

Gilson and coworkers suggested an anticorrelation of electrostatic energy and intramolecular Coulombic interaction energy.[7] (This relation also can be found in our work; see Fig. 3.) In their explanation, they indicated that side-by-side dipoles are less strongly solvated and interact more favorably with each other when antiparallel than when parallel. In addition, the anticorrelation may also result from the energetic trade-off of intramolecular peptide–peptide hydrogen bonds against peptide–solvent hydrogen bonds. In other words, it may arise from the possibility of replacing the intramolecular hydrogen bonds by hydrogen bonds between peptide and water. The intramolecular hydrogen bonds of SD and SDBEM simulations are listed in Table I. The criteria used

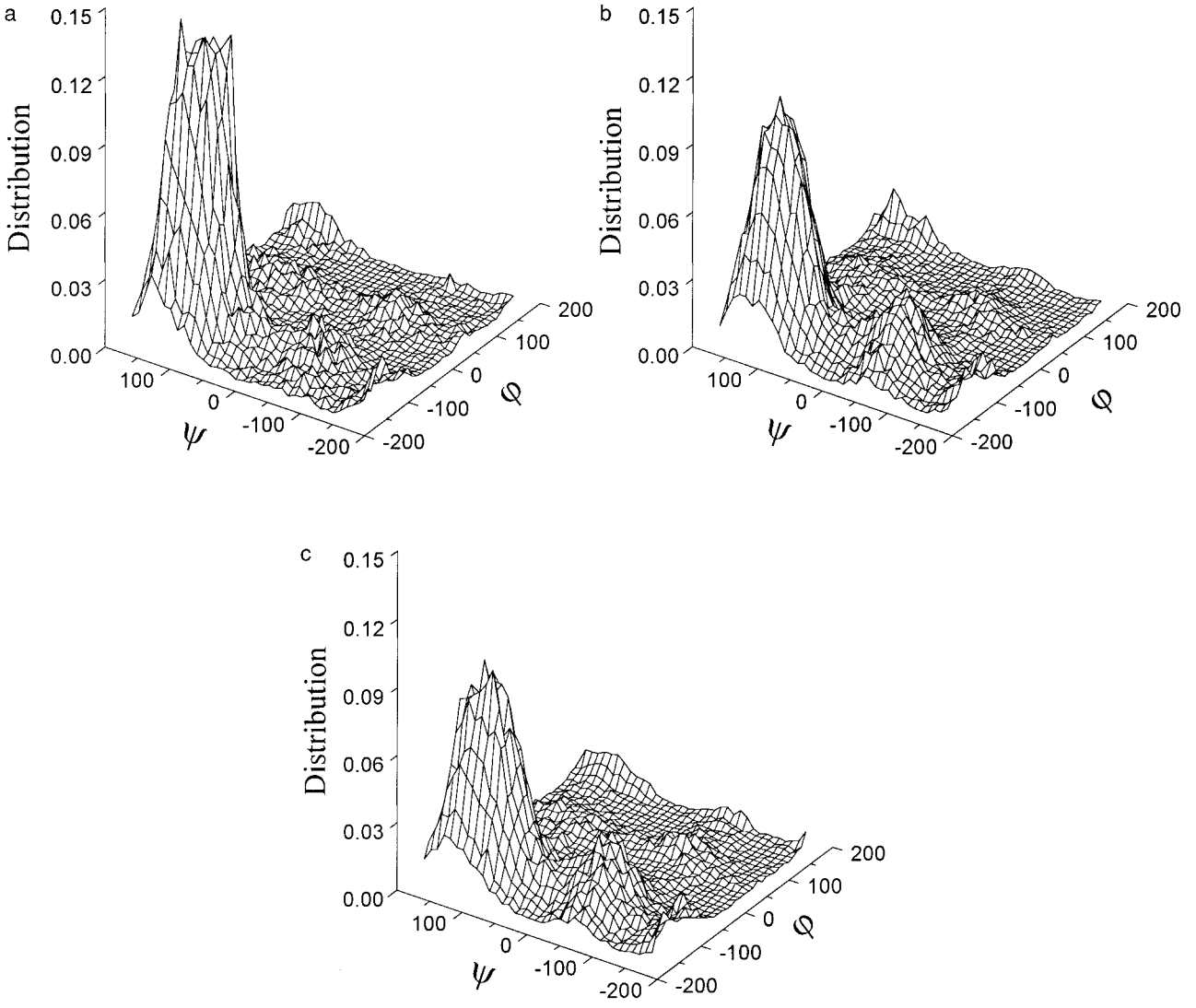

FIGURE 2. Probability distributions for dihedral angles of alanine dipeptide from (a) SD simulation and (b) SDBEM simulation with 60 triangles, and (c) with 112 triangles.

to determine an H-bond are purely geometric: for each coordinate set, every potential donor–acceptor is tested and considered to form an H-bond if the hydrogen to acceptor distance is less than 0.25 nm and the donor–acceptor angle is larger than 90°. The frequencies of H-bonds are determined from the occurrences registered on the simulation trajectory frames.

As seen in Table I, the occupancies of intramolecular hydrogen bonds of SDBEM simulations are less than those of SD simulations. This means that the SDBEM simulation decreases the formation of those H-bonds because we have added the hydration force on charge and solvent surface pressure into the mean force of the solvent in our simulation. Therefore, SDBEM simulation reflects correctly the electrostatic effects of the solvent and the competition for hydrogen bonds between internal peptide and water molecules.

TABLE I.
Frequencies of Intramolecular Hydrogen Bonds Obtained from SD and SDBEM Simulations Data of Dialanine (in Percent).

Donor	Acceptor	SD	SDBEM (60)	SDBEM (112)
N^1—H^1	O^2	13.1	8.4	10.1
N^2—H^2	O^1	10.2	6.9	6.3

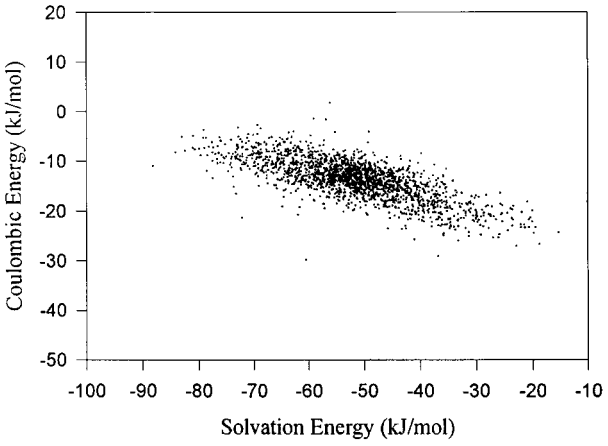

FIGURE 3. Scatterplot of electrostatic energy from BEM versus intramolecular Coulombic energy for 2-ns trajectories of SDBEM simulation.

TOTAL SOLUTION PHASE ENERGIES AND SOLVATION ENERGIES

Tables II and III list the total solution phase and solvation energies of various conformations relative to the C_7^{eq} conformation. We take the SCRF optimized values[12] of the angles φ and ψ for the dipeptide because our distribution maps cannot define them consistently. However, the α_R conformation could not be located in aqueous solution according to SCRF calculation. In our simulations there exists an obvious peak at this conformation. Therefore, we also simulate the dipeptide restrained at this conformation.

By comparing the ordering of the phase energies obtained in our simulations with the ones predicted by Gould et al.[12] and Cortis et al.[13] we find, in contrast to their results, that the C_7^{eq} structure is most favored in solution. Our results agree with the ordering of molecular orbital calculation in the presence of a reaction field,[16] except for the α_L conformation. In our simulations, the large differences of energies among different conformations may result from the high temperature used in our simulations. It is noteworthy that the α_L conformation also has the highest energy in SCRF and PCM calculations.[12,13] A more precise comparison is difficult to make at this point because there are no secure values for the ''correct'' answer. In addition, the wide range of predicted values suggests that it is not yet clear which of the theoretical estimations is the most reliable.

The SDBEM results for the solvation energy are given in Table III. The C_7^{eq}, $C_7^{\alpha x}$, and β conformations are along the ''antidiagonal'' of the Ramachandran plot, where φ and ψ are about equal in magnitude but opposite in sign. The two peptide dipoles are approximately antiparallel and the net molecular dipole is small. On the other hand, the dipoles of α_R and α_L conformations are approximately parallel and yield a large net molecular dipolar moment. Hence, the α_R and α_L conformations are more strongly solvated than other conformations. The resultant orders of solvation energies are similar for all calculations except that the β conformation in our simulations differ from those of SCRF and PCM calculations. Our results also deviate somewhat more from the integral equation results of Pettitt and Karplus,[17] as with SCRF and PCM. This may be due to the fact that the RISM calculation was present in their gas phase energy surface. The total solution phase and solvation energies are in agreement between the two SDBEM simulations using 60 and 112 triangles. It is of interest to note that, in our simulations, we consider only the electrostatic interactions. The nonpolar interactions are not included in SDBEM simulations, but are involved in the SCRF and PCM calculations. It is useful to estimate this effect in our simulations.

TABLE II.
Total Solution Phase Energies of Dialanine (All Energies in Kilocalories per Mole).

	SCRF-R[a]	PCM[a]	SCRF-PBF[b]	SDBEM (60)	SDBEM (112)	SD	HF / 3-21G[c]
C_7^{eq}	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$C_7^{\alpha x}$	0.07	−0.66	2.59	5.53	3.60	7.74	2.20
α_R	—	—	—	4.35	1.87	5.78	1.63
α_L	1.89	0.69	1.07	10.53	6.94	12.18	1.78
β	−4.27	−3.59	−1.25	6.97	3.29	3.49	—
β_2	−5.44	−1.47	−0.41	6.36	4.93	6.47	3.51

[a]From Ref. 12; [b]from Ref. 13; and [c]from Ref. 16.
—: no corresponding structure found.

TABLE III.
Solvation Energies of Dialanine (All Energies in Kilocalories per Mole).

	SCRF-R[a]	PCM[a]	SCRF-PBF[b]	SDBEM (60)	SDBEM (112)	RISM[c]
C_7^{eq}	0.00	0.00	0.00	0.00	0.00	0.00
$C_7^{\alpha x}$	0.07	−0.66	−0.32	−0.13	−0.05	−0.7
α_R	—	—	—	−2.52	−2.55	−9.9
α_L	−1.17	−2.37	−3.70	−2.39	−2.22	−10.4
β	−3.49	−2.99	−3.08	−0.73	−0.60	—
β	−5.79	−1.82	−2.91	−1.53	−1.50	—

[a]From Ref. 12; [b]from Ref. 13; and [c]from Ref. 17.
—: No corresponding structure found.

NONPOLAR INTERACTIONS

The SDBEM simulation just described does not include nonpolar interactions, a force term between a molecule with no internal partial charges and solvent. In some work, it is assumed that the nonpolar interactions are reasonably independent of conformation, so the difference in electrostatic energy will mimic the difference in total solvation energy. However, we wish to estimate the effect of this interaction term. For this purpose, we compute the solvent accessible surface area from the coordinate trajectory of the SDBEM simulation. The corresponding free energy of transfer[18] is also calculated.

The surface area and the corresponding free energy of transfer are computed using the method introduced by Richmond.[19] The surface is defined at the center of the probe rolling around the molecule. The free energy of transfer is calculated using:

$$\Delta G_R = \sum_{atom\ i} \Delta\sigma_i A_i \tag{14}$$

where $\Delta\sigma_i$ presents the atomic solvation parameters (ASPs), taken from Ref. 18. They are proportionality constants that depend upon the type of atoms. A_i is the solvent accessible surface area of atom i.

The surface area of dialanine varies between 3.17 and 4.12 nm^2 as the dihedral angles φ and ψ range independently between $-180°$ and 180°. The surface energy varies between 12.5 and 20.7 kJ/mol. Although this variation in surface energy is small compared with that in electrostatic energy (ca. 70 kJ/mol), the nonpolar interactions may be important. When the conformation of dialanine changes, the surface area varies remarkably. This causes a large variation of entropy and enthalpy of the surroundings. Hence, this fact may appreciably influence the equilibrium conformation of peptides and proteins.

Our simulation completely neglects these nonpolar contributions to the solvation effects. The solvation model is therefore incomplete. We may therefore proceed to incorporate this effect in our SDBEM simulation.

EFFECT OF DIFFERENT TRIANGLE NUMBER

To examine the effects of different triangle numbers used in SDBEM simulations, the hydration and pressure forces have been compared atom-by-atom for the two SDBEM simulations, and the following weighted averages were computed:

$$\%|\mathbf{F}| = \frac{\sum_k \|\mathbf{F}_2^k| - \mathbf{F}_1^k\|}{\sum_k |\mathbf{F}_2^k|} \times 100\% \tag{15}$$

$$\langle \Delta\theta \rangle = \frac{\sum_k |F_2^k| \cos^{-1}\left(\dfrac{\mathbf{F}_2^k \cdot \mathbf{F}_1^k}{|\mathbf{F}_2^k||\mathbf{F}_1^k|}\right)}{\sum_k |\mathbf{F}_2^k|} \tag{16}$$

where $\mathbf{F}$ represents the electrostatic force or the pressure force. The subscript indicates the two different SDBEM simulations using 60 and 112 triangles, respectively. The sum ranges over all atom indices. Eq. (15) represents the expected fractional deviation in the magnitudes of the forces computed by the two simulations, whereas eq. (16) represents the average angular deviation between the directions of the forces. For the structures selected freely from the coordinate trajectory, the deviations are similar. For the electrostatic and the pressure forces, the average differences in force magnitude are 8.82% and 2.05%, whereas the average angular deviations are 7.13° and 0.01°, indicating close agreement between the two SDBEM simulations.

Discussion

In this work, two extra mean force terms of hydration force on charge and a surface pressure of solvent determined by the BEM have been added into the SD simulation to represent the average solvent effect on the solute atoms. The reliability of this methodology has been examined. We have selected alanine dipeptide as our study target to carry out 2-ns SDBEM simulations. The analysis results have been compared with SD simulation and other theoretical and calculational results.

For alanine dipeptide, there are no secure values for the standard measures, and the wide range of predicted values suggests that it is not yet clear which of the theoretical estimates is the most reliable. However, our results are reasonable compared with other theoretical and calculational results. The results are remarkable for several reasons. One is the simplicity of the solvation model. The nonpolar interaction corresponding to solvation of a molecule in a hypothetical electrically neutral form is not included in our model. According to our calculations, this term may be important in the total solvation interaction. In addition, it is assumed that the charge distribution of solute is independent of conformation and is unaffected by solvation. Grant and coworkers[20] suggested that the effects of solute polarization and its conformational dependence can be substantial. Another reason is that we have incorporated the electrostatic force into SD simulation directly, without justifying the parameters of the SD program. Indeed, the potential energy functions will need to be reparameterized when solvation interaction is included explicitly, because the typical parameterizations of GROMOS have been skewed to artificially match experimental quantities without the inclusion of solvation interaction. The third reason is that our simulations use boundary elements that are coarsely defined. The success of the calculations implies that the systematic errors in the atomic forces which result from the use of coarse boundary elements are modest. Although there exist weaknesses, the improvement of SDBEM simulation is obviously relative to conventional SD simulation. The success of the calculation implies that SDBEM simulation offers a possible tool to study the structure and dynamic properties of biomolecules in solution.

The utility of one method will depend in part on the computational speed of the algorithm. The dialanine calculation of SDBEM simulation is, on average, about 32 times more expensive than the conventional SD simulation technique. The additional SDBEM simulation time is mainly used to generate a proper surface molecule and triangulate it. It increases with the accessible surface area of the molecule. Therefore, this additional time increases slowly with the number of atoms, N, of the molecule. On the other hand, the time of conventional SD simulation increases with the square of N. The larger the molecule, the less the proportion of additional time in total SDBEM simulation. For SDBEM simulations of CPA, the SDBEM simulations require only about 2.3 times the computational time compared with the SD simulation. Therefore, the SDBEM simulation may be more efficient for a large system. It would be worthwhile to test this approximation and to apply it in a more complex system.

Further study of this method will focus on developing the solvation model and reparameterizing the potential energy functions of SDBEM simulations. In addition, there is a need to increase calculation speed and precision of algorithms for solving the Poisson–Boltzmann equation using the BEM. We believe that with further development of algorithms it should be possible to use this method for studying large biomolecular systems without use of the cut-off radius in the calculation of electrostatic interaction.

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